Infection related to Klebsiella pneumoniae producing carbapenemase in renal transplant patients

Infecção relacionada a Klebsiella pneumoniae produtora de carbapenemase em pacientes transplantados renais

Infección relacionada con Klebsiella pneumoniae productora de carbapenemasa en pacientes trasplantados renales

**ABSTRACT**

**Objective:** To evaluate the risk factors related to Klebsiella pneumoniae carbapenemase infection after renal transplantation. **Methods:** This was a retrospective epidemiological (case-control) study, conducted from October 2011 to March 2016. Transplanted patients with infection by this bacteria during hospitalization were selected as cases. The controls were paired by age, sex, type of donor and transplant time. The proportion of cases and controls was 1:2. **Results:** Thirty hundred and five patients were included in the study (45 cases and 90 controls). The risk factors found for infection by KPC were: time of hospitalization after the transplant (OR: 4.82; CI95% 2.46-9.44), delayed kidney function (OR: 5.60; CI95% 1.91-11.01) and previous infectious for another microorganism (OR: 34.13 CI95% 3.52-132.00). **Conclusion:** The risk of acquisition of this bacterium was directly related to invasive procedures and exposure to the hospital environment. The findings reinforce the importance of prevention measures and control of infection by this microorganism.

**Descriptors:** Infection; Infection Control; Kidney Transplantation; Bacteria; Nursing Care.

**RESUMO**

**Objetivo:** Avaliar os fatores de risco relacionados à infecção por Klebsiella pneumoniae carbapenemase após o transplante renal. **Método:** Estudo retrospectivo epidemiológico (caso-controle), realizado de outubro de 2011 a março de 2016. Pacientes transplantados com infecção por essa bactéria durante a internação foram selecionados como casos. Os controles foram pareados por idade, sexo, tipo de doador e tempo de transplante. A proporção de casos e controles foi de 1:2. **Resultados:** Trinta e cinco pacientes foram incluídos no estudo (45 casos e 90 controles). Os fatores de risco para a infecção encontrados por KPC foram: tempo de hospitalização após o transplante (OR: 4,82, IC95% 2,46-9,44), função renal retardada (OR: 5,60, IC95% 1,91-11,01) e anterior infecciosa para outro microorganismo (OR: 34,13 CI95% 3,52-132,00). **Conclusão:** O risco de aquisição dessa bactéria esteve diretamente relacionado a procedimentos invasivos e exposição ao ambiente hospitalar. Os achados reforçam a importância de medidas de prevenção e controle da infecção por esse microorganismo. **Descritores:** Infecção; Controle de Infecções; Transplante Renal; Bactérias; Cuidados de Enfermagem.

**RESUMEN**

**Objetivo:** Evaluar los factores de riesgo relacionados con la infección por Klebsiella pneumoniae carbapenemasa después del trasplante renal. **Método:** Estudio retrospectivo epidemiológico (caso-control), realizado de octubre de 2011 a marzo de 2016. Pacientes transplantados con infección por esa bacteria durante la internación fueron seleccionados como casos. Los controles se parearon por edad, sexo, tipo de donante y tiempo de trasplante. La proporción de casos y controles fue de 1:2. **Resultados:** Treinta y cinco pacientes fueron incluidos en el estudio (45 casos y 90 controles). Los factores de riesgo para la infección encontrados por KPC fueron: tiempo de hospitalización después del trasplante (OR: 4,82, IC95% 2,46-9,44), función renal retardada (OR: 5,60, IC95% 1,91-11,01) y anterior infecciosa para otro microorganismo (OR: 34,13 IC95% 3,52-132,00). **Conclusión:** El riesgo de adquisición de esta bacteria estuvo directamente relacionado a procedimientos invasivos y exposición al ambiente hospitalario. Los hallazgos refuerzan la importancia de medidas de prevención y control de la infección por ese microorganismo. **Descripciones:** Infecciones; Control de Infecciones; Transplante de Riñón; Bacterias; Atención de Enfermería.


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Methods

Protocol and data collection

Data collected from patient files considered cases and controls were: sociodemographic characteristics, etiology of end stage renal disease (ESRD), laboratory tests at entry into the study, results of cultures for microorganisms according to the location of standardized collection, type and duration of dialysis treatment prior to transplant, clinical complications and death, if that occurred. For identification of the risk factors, the parameters were monitored for a period of six months preceding the date of infection or colonization by KPC, and for the controls, the six months prior to the index infection was included for risk factors analysis, occurrence of death and clinical variables of interest of the case group and control were recorded for a period of one year prior to the infection by KPC.

Patients

Transplant recipients, regardless of the time of renal transplantation, who in the occasion of hospitalization developed infection with positive culture for Klebsiella pneumoniae carbapenemase (KPC), identified by active surveillance. Active surveillance of multidrug-resistant organisms is routinely performed by the Commission for the Prevention and Control of Infection of the HrIm/FOR with patients hospitalized in this service[17]. Throughout the study period, surveillance cultures (perineal– rectal swab samples in Stuart’s transport medium) were collected from all patients admitted from other hospitals, as well as on a weekly basis from patients in intensive care units (ICUs).

Were considered cases: renal transplant recipients (TX), aged > 18 years; those who presented with infection at the initiation of the study with positive culture for KPC in one or more of the following samples: blood culture, urine culture; broncho-alveolar lavage; wound secretion with positive which KPC. Only the first infection was included for risk factors analysis, occurrence of death and clinical variables of interest of the case group and control were recorded for a period of one year prior to the infection by KPC.

Were considered controls: kidney transplant patients at the same institution and period of transplant, with age, sex, time of transplant (in days, the closest to the respective case), and donor type (live or deceased) similar to the cases, without positive culture for KPC or other type of infection at the initiation of the study. The ratio between the cases and controls was 1:2.

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in isolation, identification, culture and antimicrobial sensitivity testing. Carbapenem-resistant strains of K. pneumoniae were identified with an automated susceptibility testing system (VITEK; bioMérieux, Marcy l’Etoile, France). Minimum inhibitory concentrations (MICs) were interpreted according to the Clinical and Laboratory Standards Institute breakpoints (18).

### Statistical analysis

A descriptive analysis of the cases and controls was conducted which examined the variables of interest. Data are presented using absolute frequencies and percentages for categorical variables, and mean ± standard deviation for continuous variables. A descriptive analysis of groups of case versus control patients was conducted, considering the demographic, clinical, and laboratory parameters related to treatment. The primary results were the presence of infection by KPC at some isolated sites. The univariate analyses were performed, comparing the variables between the groups (case and control). The association between infection and categorical variables were tested with the chi-square or Fisher’s exact test, and the association between continuous variables and the presence of infection was done using the Student t**-**test, as appropriate. In the analysis of the associations, the odds ratios with confidence intervals at the 95% level were calculated. A multivariate analysis using logistic regression to investigate factors associated with infection/colonization was also performed. In this final analysis, the dependent variable was presence of infection by KPC, and the independent variables tested were those who present a value of p<0.20, in the initial univariate analyses. All analyses were performed using the Statistical Package for Social Sciences software (SPSS 17.0, Chicago, IL, USA).

### RESULTS

In the 45 patients considered cases, 277 samples were identified as positive for KPC. The site of KPC isolation in 62 % of the samples was the urine culture, 25 % blood culture, 9% surgical site infection (wound secretions) and 4% in tracheal aspirate.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n=45)</th>
<th>Controls (n=90)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>4.12 ± 12.11</td>
<td>4.62 ± 12.31</td>
<td>0.325</td>
</tr>
<tr>
<td>Male %</td>
<td>28 (61%)</td>
<td>54 (59%)</td>
<td>0.974</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>glomerulonephritis</td>
<td>18 (40%)</td>
<td>41 (45%)</td>
<td>0.304</td>
</tr>
<tr>
<td>Polycystic kidneys</td>
<td>10 (22%)</td>
<td>18 (20%)</td>
<td>0.962</td>
</tr>
<tr>
<td>Undetermined</td>
<td>4 (10%)</td>
<td>20 (22%)</td>
<td>0.038</td>
</tr>
<tr>
<td>Others</td>
<td>3 (9%)</td>
<td>11 (13%)</td>
<td>0.421</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>23 (52%)</td>
<td>41 (45%)</td>
<td>0.441</td>
</tr>
<tr>
<td>DM</td>
<td>6 (13%)</td>
<td>13 (14%)</td>
<td>0.987</td>
</tr>
<tr>
<td>Other*</td>
<td>16 (35%)</td>
<td>46 (41%)</td>
<td>0.369</td>
</tr>
<tr>
<td>Type of dialysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>41 (93%)</td>
<td>85 (94%)</td>
<td>0.953</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>3 (6%)</td>
<td>3 (3%)</td>
<td>0.235</td>
</tr>
<tr>
<td>Conservative</td>
<td>1 (1%)</td>
<td>2 (3%)</td>
<td>0.378</td>
</tr>
<tr>
<td>Time of dialysis, preceded months</td>
<td>51.32 ± 43.23</td>
<td>49.92 ± 43.11</td>
<td>0.241</td>
</tr>
<tr>
<td>Time of transplantation, months</td>
<td>23.90 ± 19.28</td>
<td>19.91 ± 18.32</td>
<td>0.117</td>
</tr>
<tr>
<td>Urea, mg/dl</td>
<td>133 ± 46</td>
<td>116 ± 43</td>
<td>0.221</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>7.34 ± 3.72</td>
<td>6.61 ± 3.21</td>
<td>0.067</td>
</tr>
<tr>
<td>Leukocytes /mm3</td>
<td>7405 ± 7348</td>
<td>883 ± 7776</td>
<td>0.085</td>
</tr>
<tr>
<td>Hemoglobin g/%</td>
<td>11.05 ± 1.75</td>
<td>11.51 ± 1.51</td>
<td>1</td>
</tr>
<tr>
<td>Hematocrit %</td>
<td>34.44 ± 5.86</td>
<td>36.96 ± 5.62</td>
<td>0.083</td>
</tr>
</tbody>
</table>

*neoplasm and systemic lupus erythematosus.

The sociodemographic characteristics, etiology of chronic renal disease (ESRD), comorbidities, type and duration of dialysis treatment before transplant, and the laboratory tests at entrance into the study of patients included in the study are presented in Table 1. There was no statistically significant difference between variables studied in the cases compared to controls and both group were considered homogeneous. Infection by KPC in patient cases occurred in 73% of the occasions during hospitalization for kidney transplant, and, in 27% of episodes that occurred in the post-transplant hospitalizations related to clinical events during the first year after the transplant in the followed up period.

### Table 2 - Characteristics of renal transplant and previous clinical complications of infection by KPC between cases and controls, São Paulo, Brazil, 2017

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases</th>
<th>Controls</th>
<th>OR (IC95%)</th>
<th>P value</th>
<th>OR (IC 95%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of donor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deceased donor</td>
<td>40 (88%)</td>
<td>83 (92%)</td>
<td>0.69 (0.28-1.71)</td>
<td>0.422</td>
<td>4.82 (2.46-9.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time of hospitalization after TX*</td>
<td>51.31 ±42.26</td>
<td>12.35±18.42</td>
<td>5.61 (2.92-10.8)</td>
<td>&lt;0.001</td>
<td>5.60 (1.91-11.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delayed kidney function</td>
<td>23 (49.3%)</td>
<td>10 (11%)</td>
<td>7.85 (4.00-15.39)</td>
<td>&lt;0.001</td>
<td>5.60 (1.91-11.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thymoglobulin induction</td>
<td>8.2 (18%)</td>
<td>4.5 (5.1%)</td>
<td>3.04 (1.14-7.91)</td>
<td>0.017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basiliximab induction</td>
<td>10 (22%)</td>
<td>5 (5%)</td>
<td>2.97 (1.19-7.10)</td>
<td>0.015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycophenolic acid</td>
<td>9 (18.8%)</td>
<td>6.39 (6.5%)</td>
<td>3.20 (1.34-7.60)</td>
<td>0.0006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
<td>7.65 (17%)</td>
<td>14.4 (16%)</td>
<td>3.20 (1.43-7.40)</td>
<td>0.689</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous infection</td>
<td>30 (65%)</td>
<td>22.5 (25%)</td>
<td>53.68 (8.00-4.00)</td>
<td>&lt;0.001</td>
<td>34.13 (3.52-132.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>26 (57%)</td>
<td>17 (19%)</td>
<td>4.96 (1.47-17.00)</td>
<td>0.004</td>
<td>2.78 (1.21-19.15)</td>
<td>0.012</td>
</tr>
<tr>
<td>CMV infection</td>
<td>14 (29%)</td>
<td>13 (19%)</td>
<td>7.60 (1.60-38.00)</td>
<td>0.003</td>
<td>9.2 (2.17-24.29)</td>
<td>0.005</td>
</tr>
<tr>
<td>Deaths</td>
<td>12 (27%)</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*TX: transplante.
In univariate logistic regression analysis the most significant events were: time of hospitalization after transplant (OR: 5.61 51.3±42.2 days versus 2.46±9.44 days, p<0.001), delayed kidney function (OR: 7.85, 49.3% versus 11%, p<0.001) and use of mycophenolic acid (OR: 3.20, 18.8% versus 6.5%, p<0.006). Clinical events were: occurrence of previous infection by other microorganisms (OR: 53.68, 65% versus 25%, p<0.001), acute rejection (OR: 4.96, 57% versus 19%, p<0.004) and cytomegalovirus infection (OR: 7.60, 29% versus 19%, p<0.003).

In the present study the mortality associated with infection KPC was 27%, a lower rate than other studies as high as 71% in recent systematic review and meta-analysis published has demonstrated that patients colonized before transplant have a higher morbidity when compared with those non-colonized patients [26].

Routine rectal swab surveillance of KPC contacts is an important measure to enhance identification and isolation of carriers associated with other interventions are more likely to be successful included minimizing use of invasive devices, promotion of antimicrobial stewardship, a standardized approach for active surveillance of at risk populations, improve the hand hygiene adherence and protocols for discontinuation of carrier status [2,27-30].

The high risk of acquiring and disseminating KPC in renal transplant patients is recommended as a component of infection control programs and the development of safe techniques for the rapid identification of this microorganism and the qPCR technique demonstrated in provides better results compared to the culture method and allows the rapid implementation of control measures and interventions to reduce the spread of health services [33].

Confronted by infectious complications in patients with ESRD, Barbosa et al.[34] evaluated the prevalence of colonization with vancomycin-resistant Enterococcus (VRE) in 300 patients on dialysis and 280 transplant recipients treated at Hospital do Rio e Hipertensão da UNIFESP. A prevalence rate of 14.5% was verified in dialysis, and of 14% in renal transplant recipients. With molecular typing of these samples, the important detection of cross-transmission of VRE among patients treated at the Serviço de Diálise e Transplante da UNIFESP (Dialysis and Transplant Service of UNIFESP) was possible[35].

Cytomegalovirus (CMV) infection is the important infectious complication in kidney transplantation, specially in the first year and it is one reason for high morbidity and mortality rates. Infection for CMV increasing the risk factors for infection by KPC related to hospitalization and invasive procedures [31].

This becomes even more important when recent studies suggest there are no differences in the survival of the patient and of the graft in renal transplant recipients receiving azathioprine or mycophenolate in combination with tacrolimus and steroids, indicating that azathioprine should be considered a therapeutic option for a selected group of patients[12].

It was observed that most donors were deceased, reflecting the national and international policies for organ donation stimulus. In recent systematic review and meta-analysis published has revealed that deceased kidney donor recipients have 20% higher risk for developing infections [36].

The risk factors found in this study should lead to greater vigilance in actions with this population, from hospital admission to discharge, especially the establishment of measures of prevention and control of infection, in particular the implementation of bundles that include washing of hands, surface cleaning, education of health staff, surveillance cultures, bathing with chlorhexidine, and contact precautions are among the key measures described to contain the spread of this bacteria [2,27,30].

Limitations of the Study

We highlight as a study limitation the fact that the majority of the patients had renal replacement therapy in other services, and because of this further analysis was not possible to deepen the analysis. Another aspect that must be emphasized is that, because it was a retrospective
study that made use of information obtained in patients’ records, the collection and insertion of data in the database analysis were confirmed by two researchers, aiming at reliability of the results.

Contributions to the Area

As implications for practice, the need for adherence to preventive measures against infections related to health care, in particular hand hygiene, are emphasized. Early identification and infection control measures for patients at higher risk of infection as delayed kidney function and risk for infection for CMV. Identification of patients colonized by KPC in this study was probably an important measure for the reduction of mortality rates, as compared to the literature.

Conclusions

The main risk factors for infection by KPC were: time of hospitalization after the transplant, delayed kidney function and clinical events that lead to the need for invasive procedures, and consequently greater exposure to the hospital environment.

Additional measures include minimizing use of invasive devices, promotion of antimicrobial stewardship, a standardized approach for active surveillance of at risk populations, and protocols for discontinuation of carrier status.

Competing interests

The authors declare that they have no competing interests.

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